VIII. Chronic Myelogenous Leukemia Research Program

Vision: To perfect the existing and develop new diagnostic and therapeutic approaches for chronic myelogenous leukemia.

Mission: To sponsor basic and clinically oriented research in the field of chronic myelogenous leukemia.

Congressional Appropriations for Peer Reviewed Research:

- $5M in FY02
- $4.25M in FY03
- $4.25M in FY04

Funding Summary:

- 6 awards from the FY02 appropriation
- 22 awards from the FY03 appropriation
- ~4 anticipated awards from the FY04 appropriation

developing new therapeutics

The Disease

Chronic myelogenous leukemia (CML) is also known as chronic granulocytic leukemia or chronic myeloid leukemia. CML is an overgrowth of granulocytes, a type of white blood cell; its cause is unknown. The disease accounts for about 14% of adult leukemias in Western countries. In 2004, approximately 4,600 individuals will be diagnosed with CML, and an estimated 1,570 will die from the disease.[1] In most cases, CML is characterized by a chromosomal abnormality that is known as the Philadelphia chromosome. Treatment usually consists of various chemotherapeutic agents used to disrupt the production of leukemic cells. These treatments may be followed by stem cell transplant. More recently, targeted therapy for CML with ST1571 (Gleevec™), an Abl-specific tyrosine kinase inhibitor, has shown significant activity, including elimination of the causative genetic defect, in patients with advanced disease. However, resistance to this therapy has been observed, indicating research is still needed.

Program Background

The Department of Defense (DOD) Chronic Myelogenous Leukemia Research Program (CMLRP) was established in fiscal year 2002 (FY02) by Joint Appropriations Conference Committee Report No. 107-350, which provided $5 million (M) for CML research. The CMLRP has managed $13.5M through FY04 to fund peer reviewed research, and 28 awards have been made through FY03 in basic and clinically oriented research to improve the diagnostic and therapeutic approaches to CML. Appendix B, Table B-6, summarizes the congressional appropriations and the investment strategy executed by the CMLRP for FY03–04.

The Fiscal Year 2003 Program

Congress appropriated $4.25M to continue the CMLRP in FY03. Due to the abundance of scientifically meritorious proposals received in FY02, a portion of the $4.25M appropriation was used to fund four Investigator-Initiated Research proposals received in FY02. In addition, a new award mechanism was created, the Exploration – Hypothesis Development Award, to expend the remaining $1.7M in FY03 funds. This mechanism was designed to support the initial exploration of innovative, untested, and potentially groundbreaking concepts in CML research. Successfully completed Exploration – Hypothesis Development Awards are expected to lead to high-risk, potentially high-gain future research endeavors submitted to this and other funding agencies. Additional information on this new award mechanism can be found in the box story on page VIII-5.

Table VIII-1. Funding Summary for the FY03 CMLRP

Category & Award	Proposals	Awards	Investment
Research			
Exploration – Hypothesis Development	64	18	$1.7M
Investigator-Initiated Research	NA[a]	4	$2.1M
Total	**64**	**22**	**$3.8M**

[a] Not applicable

[1] National Cancer Institute Physician Data Query and American Cancer Society - *Cancer Facts and Figures,* 2004.

"...[the CMLRP] is a very important program that will result in important new discoveries towards the treatment of leukemias..."

Leonidas C. Platanias, M.D., Ph.D., FY03 Peer Review Panel Chair

Table VIII-1 provides a summary of the FY03 CMLRP award categories and mechanisms in terms of number of proposals received, number of awards, and dollars invested. As illustrated in Figure VIII-1, the FY03 CMLRP has supported a multidisciplinary portfolio of research.

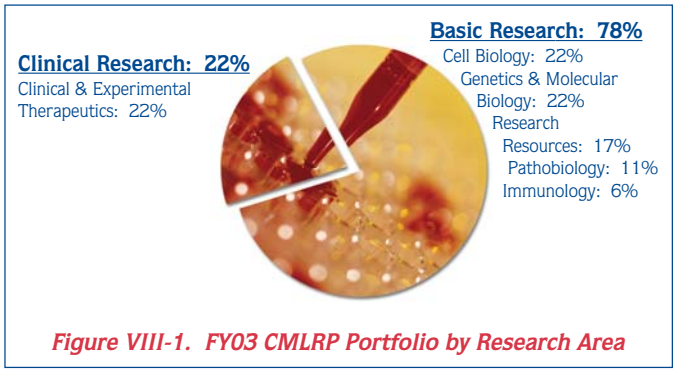


Figure VIII-1. FY03 CMLRP Portfolio by Research Area

The Vision for the Fiscal Year 2004 Program

The CMLRP was continued through an FY04 congressional appropriation of $4.25M. A new award mechanism, called the Therapeutic Development Award, was launched to move the field significantly closer to the development of new therapeutics for CML. Therapeutic Development Awards are intended to support any and all preclinical phases of development of potential CML-specific therapeutic agents. The overall goal is to allow CML investigators to develop the means to analyze preclinical efficacy of novel and existing agents and/or to generate preclinical data necessary to conduct clinical trials after completion of the proposed work. For the FY04 program, a total of 23 proposals were received, as detailed in Table VIII-2, and approximately 4 awards are anticipated.

Scientific Outcomes and Advances

While the first awards to CMLRP investigators were made in FY02, research funded by this new program is already producing results. The following project represents the efforts of one CMLRP-supported investigator who is laying the groundwork for new therapeutic strategies for the treatment of CML.

Overcoming Imatinib-Resistant Chronic Myelogenous Leukemia with Combinatorial Therapy

Steven Grant, M.D., Virginia Commonwealth University

Imatinib (Gleevec™) revolutionized the treatment of CML by targeting the tyrosine kinase Bcr/Abl fusion protein found in 95% of leukemia cells of CML patients. However, as many as 20% of CML patients have or develop resistance to Imatinib, which arises from mutations in Bcr/Abl not recognized by the drug. Thus, current efforts are focused on non-Bcr/Abl-dependent molecular pathways to control Imatinib-resistant CML. Among those leading the effort is Dr. Steven Grant, an FY02 CMLRP Investigator-Initiated Research Award recipient, who is investigating interactions between a class of agents called histone deacetylase inhibitors (HDACIs) and two other clinically relevant drugs, the proteasome inhibitor, bortezomib, and the cyclin-dependent kinase inhibitor, flavopiridol, in Imatinib-sensitive and -resistant Brc/Abl-positive CML cell lines. HDACIs promote the expression of proteins involved in various cellular processes through DNA modification and subsequent chromosomal remodeling. Proteasome inhibitors may increase the stability of proteins by slowing their degradation while cyclin-dependent kinase inhibitors interfere with the normal progression of cellular division. These agents, singularly or in combination, can induce cellular suicide, a process known as apoptosis; however, their effect in CML remains unexplored. Combinations of HDACIs + bortezomib or bortezomib + flavopiridol, at minimally toxic or subtoxic concentrations, synergistically induced apoptosis in Bcr/Abl-positive CML cell lines, including cells resistant to Imatinib. Both treatment combinations increased cellular mitochondrial injury and reactive oxygen species, down-regulated the mitogen-activated protein kinase cell signaling pathway, and decreased nuclear factor kappaB activity; all of which are

Table VIII-2. Award Mechanisms Offered and Proposals Received for the FY04 CMLRP

Category & Award	Proposals
Research	
Therapeutic Development	23
Total	**23**

"...the consumer reviewers were an inspiration to all of the scientists on the panel...we helped them see why what they do is so important."

David Cranmer, FY03 Consumer Peer Review Member

A Consumer's Perspective: David Cranmer

I am a five-year survivor of CML. I had a bone marrow transplant in 2000 and have been in molecular remission for the past three years.

I was originally invited to the CML Peer Review Panel in November of 2002. The Leukemia and Lymphoma Society nominated me, due to my involvement in delivering patient services in the state of Vermont. I was pleased and honored when the CDMRP asked me to participate in a second Peer Review Panel in April 2004.

I am not a scientist [and], in fact, did not know much about medical research until my diagnosis. As a patient, I realized there was a need for more information and more support for those who are dealing with cancer. Since my diagnosis, I have done my own research and have learned much from the people I have met that are involved with leukemia – scientists, health care professionals, and other patients.

The entire Peer Review process (both the review of the proposals and the actual panel meetings) was very inspiring to me as a patient. It allowed me to learn more about my disease, and to see how much progress medical research has already made in finding a cure. More importantly, it demonstrated how much more work is needed.

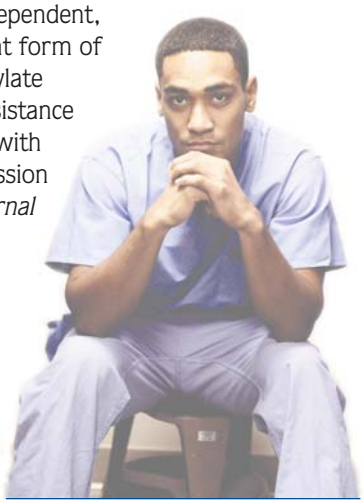
I was impressed by the number of people involved in the research programs that were requesting funding, and by the quality of their work. I was even more impressed by the individuals who were serving on the [Peer Review] Panel with me. I was told by many of the scientists that the consumer reviewers (the three CML survivors on the panel) were an inspiration to all of the scientists on the panel…that we helped them see why what they do is so important. My reply was that they were an inspiration to me. The intelligence and commitment of everyone on the panel – all extremely dedicated to finding a cure – has convinced me that there will soon be a cure for CML.

It is this message of hope that I brought back from the panel and continue to share with the people in my community.

involved in apoptosis induction. Bortezomib + flavopiridol also down-regulated Bcr/Abl protein levels and diminished the activity of factors involved in producing Bcr/Abl. Ongoing efforts are focused on determining efficacy of these combinatory treatments in primary CML cells obtained from patients sensitive and resistant to Imatinib and elucidating the molecular mechanisms of these effects. These studies may provide a platform for the development of novel combinatorial therapeutics for the treatment of Imatinib-resistant CML.

Additional information about this research can be found in the following publications:

- Yu C, Rahmani M, Conrad D, et al. 2003. The proteasome inhibitor bortezomib interacts synergistically with histone deacetylase inhibitors to induce apoptosis in Bcr/Abl+ cells sensitive and resistant to STI571. *Blood* 102(10):3765–3774.
- Dai Y, Rahmani M, Pei XY, et al. 2004. Bortezomib and flavopiridol interact synergistically to induce apoptosis in chronic myeloid leukemia cells resistant to Imatinib mesylate through both Bcr/Abl-dependent and -independent mechanisms. *Blood* 104(2): 509–518.
- Dai Y, Rahmani M, Corey SJ, et al. 2004. A Bcr/Abl-independent, Lyn-dependent form of Imatinib mesylate (STI-571) resistance is associated with altered expression of Bcl-2. *Journal of Biological Chemistry* 279:34227–34239.



"These awards will make a significant impact on CML research and treatment, building on the exciting results of kinase inhibitor therapy in CML."

Richard A. Van Etten, M.D., Ph.D.

Exploring New Ideas in Research

A closer look at the CMLRP Exploration – Hypothesis Development Award mechanism reflects the Program's investment in providing opportunities for innovative, untested, and potentially groundbreaking research. This mechanism was adopted from the Prostate Cancer Research Program's mechanism of the same name. Several key features of this mechanism included the following: support for the exploration of potentially groundbreaking concepts, investigators at all levels were eligible to apply, preliminary data were not required, feasibility/plausibility was considered in the review criteria, and expedited or exempt institutional review board (IRB) status was required. The IRB status was included to provide a quick negotiation process because of the impending September 30, 2004 deadline for obligation of FY03 funds. A total of 64 proposals were received from which 18 were funded. These awards cover a spectrum of topics including studies related to the natural history of CML, genetic instability in CML, novel animal models of CML, and innovative therapeutics for CML. It is anticipated that the Program's investment in these innovative hypotheses will result in important outcomes for CML patients.

Bottom Line

Since FY02, the DOD CMLRP has been responsible for managing $13.5M in congressional appropriations, resulting in 28 awards through FY03. Projects funded by this newly established program are anticipated to improve the understanding of the basic science of CML, advance the diagnostic and therapeutic approaches to CML, and enhance the quality of life for individuals and their families living with the disease. Research highlights, award data, and abstracts of funded CMLRP proposals can be viewed on the Congressionally Directed Medical Research Programs website (http://cdmrp.army.mil).

Fiscal Year 2004 Integration Panel Members

Moshe Talpaz, M.D. (Chair), M.D. Anderson Cancer Center

Alan Kinniburgh, Ph.D., The Leukemia & Lymphoma Society

Rose McCullough, Ph.D., Consumer, most recently served as Executive Director of the AIDS Vaccine Advocacy Coalition

Janet Rowley, M.D., University of Chicago

Richard A. Van Etten, M.D., Ph.D., Tufts-New England Medical Center

Signs and Symptoms

CML can be divided into three phases called chronic, accelerated, and acute depending on the maturity of the leukemia white blood cells. Symptoms of CML usually develop gradually over time. In the early stage of CML (chronic), there are usually no symptoms of leukemia present. However, as CML progresses, symptoms may be present but are often nonspecific and gradual in onset. Such signs may include weakness, fatigue, fever, poor appetite, weight loss, increased sweating, and an enlarged spleen. In the acute phase, also called the blast phase, significant symptoms are usually experienced that may include weight loss, anemia, fever, bone pain, and recurring infections.